Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

Claims 1-25. (canceled)

Claim 26. (currently amended) An isolated antibody, or an antigen-binding portion thereof, capable of binding human IL-18, wherein said antibody or antigen–binding portion thereof comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a heavy chain CDR1 domain of SEQ ID NO: 9 or modified from SEQ ID NO: 9 by at least one amino acid substitution at a position selected from the group consisting of H30, H31, H32, H33, and H35, wherein the amino acid substitution at H30 is selected from the group consisting of A, R, N, D, C, G, H, I, F, P, S, and V; wherein the amino acid substitution at H31 is selected from the group consisting of A, C, H, S, T, and Y; wherein the amino acid substitution at H32 is selected from the group consisting of R, N, C, H, P, S, and T; wherein the amino acid substitution at H33 is selected from the group consisting of N, D, C, Q, H, L, M, F, S, and V; and wherein the amino acid substitution at H34 is selected from the group consisting of N, D, L, and F;

a heavy chain CDR2 domain of SEQ ID NO: 10 or modified from SEQ ID NO: 10 by at least one amino acid substitution at a position selected from the group consisting of H52, H52a, H53, H54, H56, and H58, wherein the amino acid substitution at H52 is T; wherein the amino acid substitution at H52a is selected from the group consisting of R, Q, L, S, T and W; wherein the amino acid substitution at H53 is selected from the group consisting of A, R, N, L, P, S, and Y; wherein the amino acid substitution at H54 is selected from the group consisting of A, R, N, D, Q, L, K, M, P, S, and Y; wherein the amino acid substitution at H56 is selected from the group consisting of A, R, N, C, G, H, I, L, and F; and wherein the amino acid substitution at H58 is selected from the group consisting of A, R, Q, E, H, I, L, K, M, F, S, T, Y, P, S, T, W, Y, and V; and

a heavy chain CDR3 domain of SEQ ID NO: 11 or modified from SEQ ID NO: 11 by at least one amino acid substitution at a position selected from the group consisting of H95, H96, H97, and H98, wherein the amino acid substitution at H95 is A, R, E, Q, S, Y, V, H, P, W, and C; wherein the amino acid substitution at H96 is selected from the group consisting of A, R, Q, S, Y, V, H, P, W and C; wherein the amino acid substitution at H97 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W, and C; and wherein the amino acid substitution at H98 is selected from the group consisting of R, E, Q, S, Y, V, H, P, W, and C; and

wherein said antibody or antigen–binding portion thereof comprises a light chain variable region comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a light chain CDR1 domain of SEQ ID NO: 12 or modified from SEQ ID NO: 12 by at least one amino acid substitution at a position selected from the group consisting of L30, L31, L32, and L34, wherein the amino acid substitution at L30 is selected from the group consisting of N, D, C, G, I, L, S, W, and Y; wherein the amino acid substitution at L31 is selected from the group consisting of R, N, D, C, G, H, I, L, P, S, T, and Y; wherein the amino acid substitution at L32 is selected from the group consisting of R, N, D, E, G, I, L, P, S, T, and V; and wherein the amino acid substitution at L34 is selected from the group consisting of A, R, N, D, E, H, I, L, K, M, F, P, S, T, Y and V;

a light chain CDR2 domain of SEQ ID NO: 13 or modified from SEQ ID NO: 13 by at least one amino acid substitution at a position selected from the group consisting of L50, L52, L53, and L55, wherein the amino acid substitution at L50 is A, N, I, L, F, P, S, W, Y and V; wherein the amino acid substitution at L52 is selected from the group consisting of A, R, D, E, H, I, L, M, F, P, S, T, and V; wherein the amino acid substitution at L53 is selected from the group consisting of A, R, C, I, L, K, M, P, S and T; wherein the amino acid substitution at L55 is selected from the group consisting of A, R, N, D, C, G, H, I, L, S, T, and Y; and

a light chain CDR3 domain of SEQ ID NO: 14 or modified from SEQ ID NO: 14 by at least one amino acid substitution at a position selected from the group consisting of L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, and L97, wherein the amino acid substitution at L89 is A, R, E, Q, S, Y, V, H, P, W, and C; wherein the amino acid substitution at L90 is selected from the group consisting of A, R, E, Q, Y, V, H, P, W and C; wherein the amino acid substitution at L91 is selected from the group consisting of R, E, Q, S, Y, V, H, P, W, and C; and wherein the amino acid substitution at L92 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W, and C; wherein the amino acid substitution at L93 is A, R, E, Q, Y, V, H, P, W, and C; wherein the amino acid substitution at L94 is selected from the group consisting of A, R, E, Q, Y, V, H, P, W and C; wherein the amino acid substitution at L95 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W, and C; and wherein the amino acid substitution at L95a is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W, and C; wherein the amino acid substitution at L95b is A, R, E, Q, S, Y, V, P, W, and C; wherein the amino acid substitution at L96 is selected from the group consisting of A, R, E, Q, S, Y, H, P, W and C; and wherein the amino acid substitution at L97 is selected from the group consisting of A, R, E, Q, S, Y, H, P, W, and C; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: ~~33~~36.

Claim 27. (canceled)

Claim 28. (canceled)

Claim 29. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising one heavy chain variable region and one light chain variable region, at least one of said variable regions comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 16, and 17, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 30. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO: 16, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 31. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 15 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 17, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 32. (canceled)

Claim 33. (currently amended) An isolated antibody, or an antigen-binding portion thereof, capable of binding human IL-18, wherein said antibody or antigen–binding portion thereof comprises a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a heavy chain CDR1 domain of SEQ ID NO: 20 or modified from SEQ ID NO: 20 by at least one amino acid substitution at a position selected from the group consisting of H31, H32, H33, and H35;

a heavy chain CDR2 domain of SEQ ID NO: 21 or modified from SEQ ID NO: 21 by at least one amino acid substitution at a position selected from the group consisting of H50, H51, H52, H52a, H53, H54, H56, and H58; and

a heavy chain CDR3 domain of SEQ ID NO: 22 or modified from SEQ ID NO: 22 by at least one amino acid substitution at a position selected from the group consisting of H95, H96, H97, H98, H99, H100, H100a, H101, and H102, wherein the at least one amino acid substitution is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W and C; and

wherein said antibody or antigen–binding portion thereof comprises a light chain variable region comprising a CDR1, a CDR2, and a CDR3 domain selected from the group consisting of:

a light chain CDR1 domain of SEQ ID NO: 23 or modified from SEQ ID NO: 23 by at least one amino acid substitution at a position selected from the group consisting of L30, L31, L32, and L34, wherein said substitution in L30 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W and C; wherein said substitution in L31 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W and C; wherein said substitution in L32 is selected from the group consisting of R, E, Q, S, Y, V, H, P, W C, and G; and wherein said substitution in L34 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W and C;

a light chain CDR2 domain of SEQ ID NO: 24 or modified from SEQ ID NO: 24 by at least one amino acid substitution at a position selected from the group consisting of L50, L52, L53, and L55, wherein said substitution in L50 is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W and C; wherein said substitution in L52 is selected from the group consisting of A, R, E, S, Y, V, H, P, W, and C; wherein said substitution in L53 is selected from the group consisting of A, R, E, S, Y, V, H, P, W C, and N; and wherein said substitution in L54 is selected from the group consisting of A, E, Q, S, Y, V, H, P, W and C; and

a light chain CDR3 domain of SEQ ID NO: 25 or modified from SEQ ID NO: 25 by at least one amino acid substitution at a position selected from the group consisting of L89, L90, L91, L92, L93, L94, L95, L95a, L95b, L96, and L97, wherein said substitution is selected from the group consisting of A, R, E, Q, S, Y, V, H, P, W, and C; wherein the at least one amino acid substitution does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of ~~SEQ ID NO: 3 and~~ SEQ ID NO: 33.

Claim 34. (canceled)

Claim 35. (canceled)

Claim 36. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising one heavy chain variable region and one light chain variable region, at least one of said variable regions comprising an amino acid selected from the group consisting of SEQ ID NO: 26, 27, and 29.

Claim 37. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 29

and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 26, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claim 38. (previously presented) An isolated antibody, or an antigen-binding portion thereof, comprising a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 29 and a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 27, wherein said isolated human antibody, or said antigen-binding portion thereof is capable of binding human IL-18.

Claims 39-52 (canceled)

Claim 53. (withdrawn) A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the antibody, or an antigen-binding portion thereof, of any one of claims 26, 29-31, 33, and 36-38, such that human IL-18 activity is inhibited.

Claim 54. (withdrawn) A method for inhibiting human IL-18 activity comprising contacting human IL-18 with the antibody, or antigen-binding portion thereof, of any of claims 26, 29-31, 33, and 36-38, such that human IL-18 activity is inhibited.

Claim 55. (withdrawn) A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the antibody, or an antigen-binding portion thereof, of any one of claims 26, 29-31, 33, and 36-38, such that human IL-18 activity in the human subject is inhibited.

Claim 56. (withdrawn) A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental, comprising administering to the human subject the antibody, or antigen-binding portion thereof, of any of claims 26, 29-31, 33, and 36-38, such that human IL-18 activity in the human subject is inhibited.

Claim 57. (withdrawn) A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental by administering the antibody, or an antigen-binding portion thereof, of any one of claims 26, 29-31, 33, and 36-38, such that said inhibiting is achieved.

Claim 58. (withdrawn) A method for inhibiting human IL-18 activity in a human subject suffering from a disorder in which IL-18 activity is detrimental by administering an antibody, or antigen-binding portion thereof, of any one of claims 26, 29-31, 33, and 36-38, such that said inhibiting is achieved.

Claim 59. (withdrawn) The method of claim 57 or 58, wherein said disorder is selected from the group comprising rheumatoid arthritis, osteoarthritis, juvenile chronic arthritis, Lyme arthritis, psoriatic arthritis, reactive arthritis, spondyloarthropathy, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, inflammatory bowel disease, insulin dependent diabetes mellitus, thyroiditis, asthma, allergic diseases, psoriasis, dermatitis scleroderma, graft versus host disease, organ transplant rejection, acute or chronic immune disease associated with organ transplantation, sarcoidosis, atherosclerosis, disseminated intravascular coagulation, Kawasaki's disease, Grave's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpurea, microscopic vasculitis of the kidneys, chronic active hepatitis, uveitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, Parkinson's disease, Alzheimer's disease, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, heart failure, myocardial infarction, Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult respiratory distress syndrome, alopecia, alopecia areata, seronegative arthopathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, spondyloarthopathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis C, common varied immunodeficiency, common variable hypogammaglobulinaemia, dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, connective tissue disease associated interstitial lung disease, mixed connective tissue disease associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated

lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis, classical autoimmune or lupoid hepatitis, type-2 autoimmune hepatitis, anti-LKM antibody hepatitis, autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthrosis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia, renal disease NOS, glomerulonephritides, microscopic vasulitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, all subtypes of multiple sclerosis, sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, idiopathic thrombocytopaenia, autoimmune thyroid disease, hyperthyroidism, goitrous autoimmune hypothyroidism or Hashimoto's disease, atrophic autoimmune hypothyroidism, primary myxoedema, phacogenic uveitis, primary vasculitis ,vitiligo, acute liver disease, chronic liver diseases, allergy and asthma, mental disorders, depression, schizophrenia, and Th2 Type and Th1 Type mediated diseases.

Claim 60. (withdrawn) A method of inhibiting human IL-18 activity in a patient suffering from a disorder in which IL-18 is detrimental comprising the step of administering the anti-IL-18 antibody, or antigen-binding portion thereof according to any one of claims 26, 29-31, 33, and 36-38, before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an anti-IL-12 antibody or antigen binding fragment thereof, methotrexate, anti-TNF antibody or antigen binding fragment thereof, corticosteroids, cyclosporin, rapamycin, FK506, and non-steroidal anti-inflammatory agents.

Claim 61. (canceled)